M. Cordero Garcia
10/886755


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=> dis his

     (FILE 'HOME' ENTERED AT 15:09:47 ON 04 APR 2005)

     FILE 'REGISTRY' ENTERED AT 15:10:08 ON 04 APR 2005
L1              STRUCTURE UPLOADED
L2            0 S L1
L3           20 S L1 FUL

=> d l3 que stat;fil caplus;s l3
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.
L3           20 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED     44 ITERATIONS                          20 ANSWERS
SEARCH TIME: 00.00.01



COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   164.34     164.55

FILE 'CAPLUS' ENTERED AT 15:14:46 ON 04 APR 2005
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FILE COVERS 1907 - 4 Apr 2005  VOL 142 ISS 15
FILE LAST UPDATED: 3 Apr 2005  (20050403/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


L4           3 L3

=> d 1-3 ibib abs hitstr;fil caol;s l3
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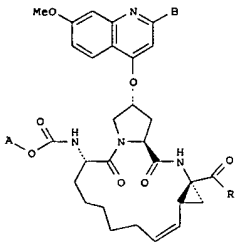
L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:192478 CAPLUS
DOCUMENT NUMBER: 140:400031
TITLE: Macrocyclic compound-containing compositions for the treatment of infection by Flaviviridae viruses
INVENTOR(S): Lamarre, Daniel; Lagace, Lisette
PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004039833	A1	20040513	WO 2003-CA1634	20031024
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2002-421900P P 20021029
US 2003-442769P P 20030127

OTHER SOURCE(S): MARPAT 140:400031
GI



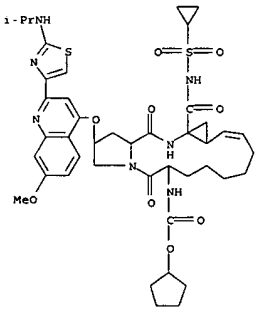
I

AB The invention relates to macrocyclic compds. I [A is alkyl or cycloalkyl;

L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
B is Ph or thiazolyl, which may be substituted by alkylamino or alkanoylamino; R is OH or NHSO2R2, where R2 is (un)substituted alkyl, cycloalkyl or aryl] or their pharmaceutically-acceptable salts for the treatment of a mammal infected with a virus of the Flaviviridae family. Thus, IC50 values for compd. I [A is cyclopentyl, B is 2-(isopropylamino)-4 thiazolyl, R is OH] against HCV NS3-NS4A protease are
shown graphically.

IT **552335-24-7 681145-23-3 681145-24-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(macrocyclic compound-containing compns. for treatment of infection by Flaviviridae viruses)

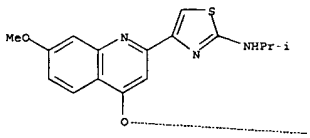
RN 552335-24-7 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-14a-[[(cyclopropylaulfonyl)amino]carbonyl]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl] 4-quinolinyl]oxy]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)



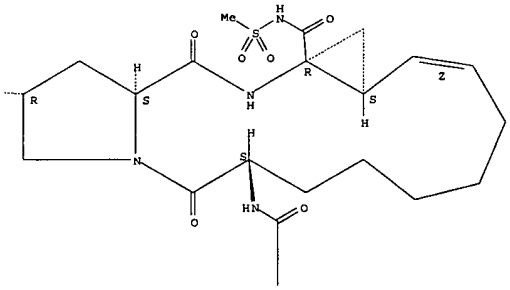
RN 681145-23-3 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-14a-[[(methylsulfonyl)amino]carbonyl]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

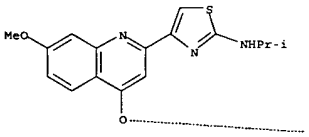


PAGE 2-B

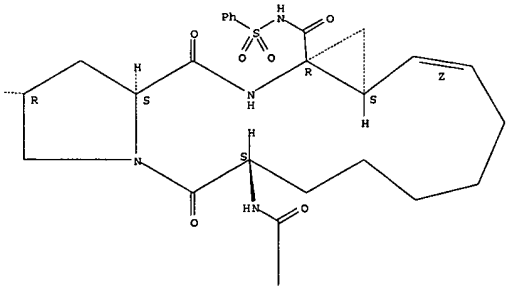
RN 681145-24-4 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-14a-[[(phenylsulfonyl)amino]carbonyl]cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 2-B

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:370958 CAPLUS
DOCUMENT NUMBER: 140:357673
TITLE: Preparation of macrocyclic peptides active against the hepatitis C virus
INVENTOR(S): Llinas-Brunet, Montse; Bailey, Murray D.
PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.h., Germany
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

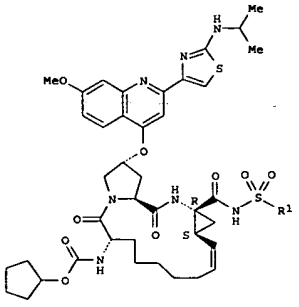
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037855	A1	20040506	WO 2003-CA1604	20031020

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
US 2002-421414P	P	20021025
US 2002-433820P	P	20021216
US 2003-442768P	P	20030127

OTHER SOURCE(S): MARPAT 140:357673
GI

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



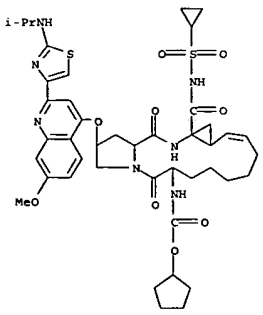
I

AB Macrocyclic peptides I [R1 is (un)substituted alkyl, cycloalkyl, alkylcycloalkyl, aryl or heteroaryl] or their pharmaceutically-acceptable salts were prepared as inhibitors of the hepatitis C virus (HCV) NS3 protease. Thus, I (R = Me) was prepared by a multistep sequence involving peptide coupling, olefin metathesis to form the macrocycle and methanesulfonamidation.

IT **552335-24-7P 681145-23-3P 681145-24-4P**
681145-25-5P 681145-26-6P 681145-27-7P
681145-28-8P 681145-29-9P 681145-30-2P
681145-32-4P 681145-33-5P 681145-34-6P
681145-35-7P 681145-36-8P 681145-37-9P
681145-38-0P 681145-39-1P 681145-40-4P
681145-41-5P 681145-42-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic peptides active against the hepatitis C virus)

RN 552335-24-7 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-14a-[[(cyclopropylsulfonyl)amino]carbonyl]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

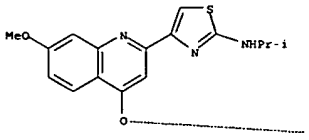
L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 681145-23-3 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-14a-[[(methylsulfonyl)amino]carbonyl]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

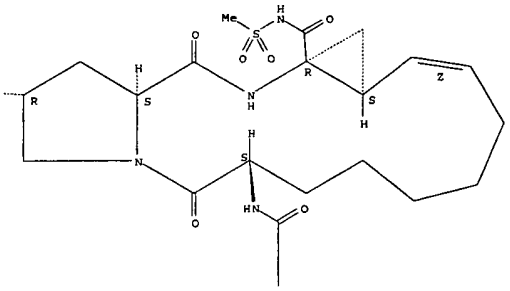
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-B



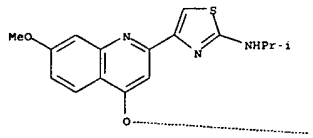
PAGE 2-B

RN 681145-24-4 CAPLUS
CN Carbamic acid,
[(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-14a-[[(phenylsulfonyl)amino]carbonyl]cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-A



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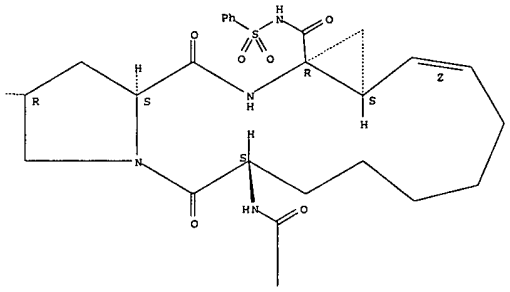


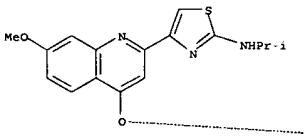
PAGE 2-B

RN 681145-25-5 CAPLUS
CN Carbamic acid,
[(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-14a-[[(4-morpholinylsulfonyl)amino]carbonyl]cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-A



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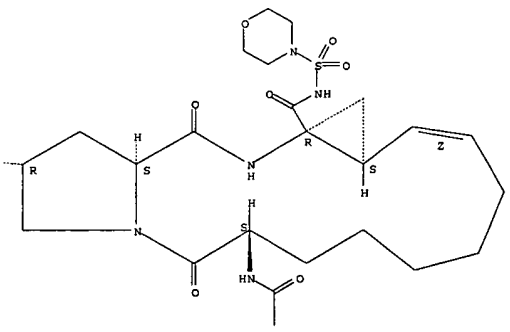


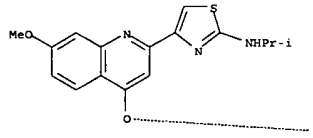
L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 2-B

RN 681145-26-6 CAPLUS
CN Carbamic acid,
[(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-14a-[[[(4-methyl-1-piperazinyl)sulfonyl]amino]carbonyl]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

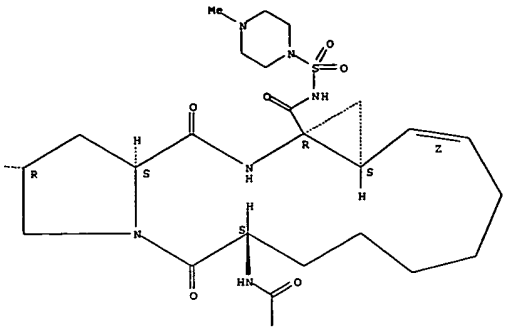
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-B



PAGE 2-B

RN 681145-27-7 CAPLUS
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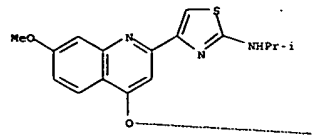
Absolute stereochemistry.
Double bond geometry as shown.

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-A



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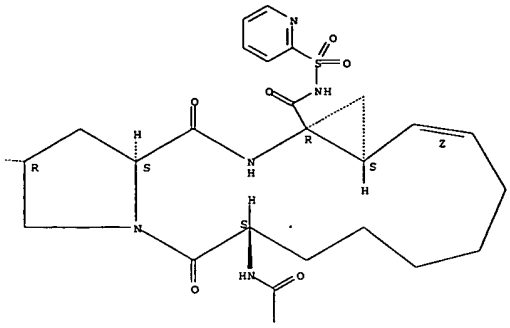
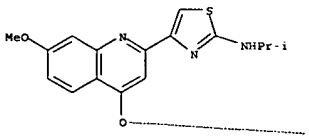


PAGE 2-B

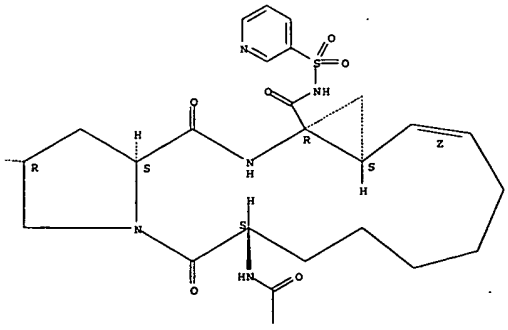
L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
RN 681145-28-8 CAPLUS
CN Carbamic acid,
[(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-14a-[[(3-pyridinylsulfonyl)amino]carbonyl]cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



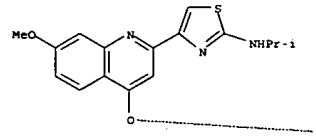
L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 2-B

RN 681145-29-9 CAPLUS
CN Carbamic acid,
[(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-14a-[[(4-pyridinylsulfonyl)amino]carbonyl]cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

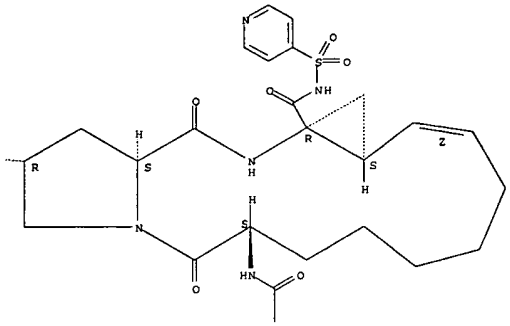
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-B



PAGE 2-B

RN 681145-30-2 CAPLUS
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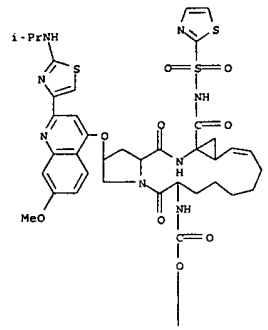
L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-A



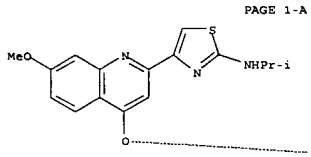
PAGE 2-A

RN 681145-32-4 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-14a-[[(ethylsulfonyl)amino]carbonyl]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

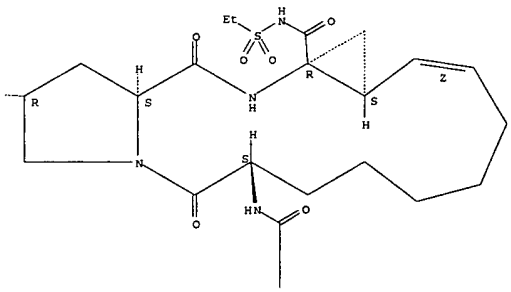
Absolute stereochemistry.
Double bond geometry as shown.

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-A



PAGE 1-B



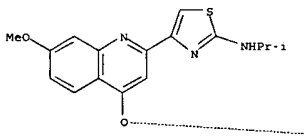
PAGE 2-B

RN 681145-33-5 CAPLUS
CN Carbamic acid,
[(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-14a-[[(propylsulfonyl)amino]carbonyl]cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

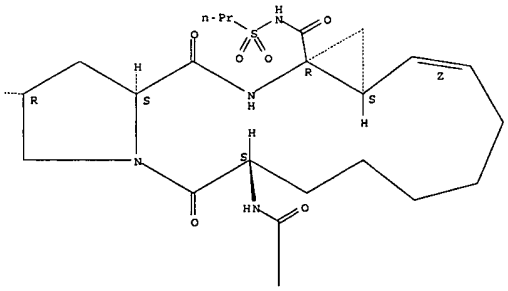
L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



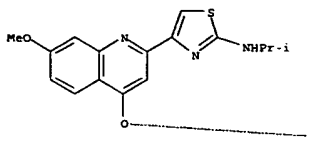
PAGE 2-B

RN 681145-34-6 CAPLUS

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-14a-[[[[(1-methylethyl)sulfonyl]amino]carbonyl]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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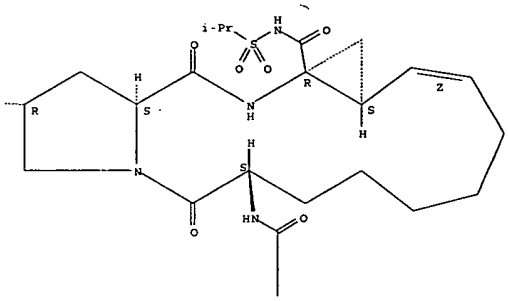


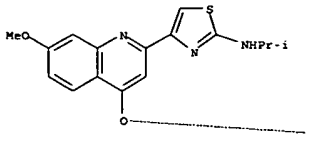
L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 2-B

RN 681145-35-7 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-14a-[[(cyclobutylsulfonyl)amino]carbonyl]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

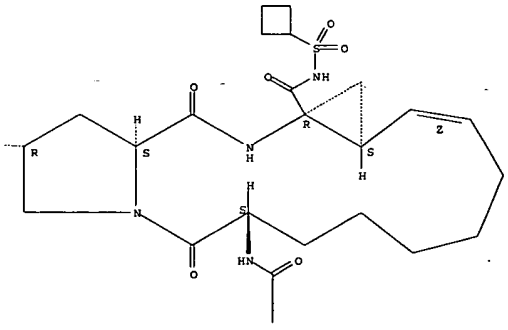
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-B

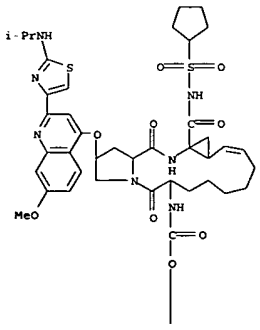


PAGE 2-B

RN 681145-36-8 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-14a-[[(cyclopentylsulfonyl)amino]carbonyl]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-A



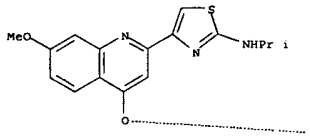
PAGE 2-A

RN 681145-37-9 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-14a-[[[(cyclopropylmethyl)sulfonyl]amino]carbonyl]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

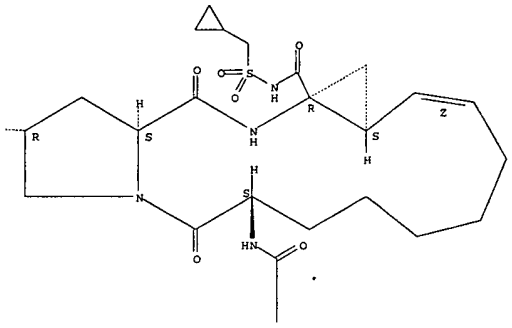
Absolute stereochemistry.
Double bond geometry as shown.

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1 A



PAGE 1-B



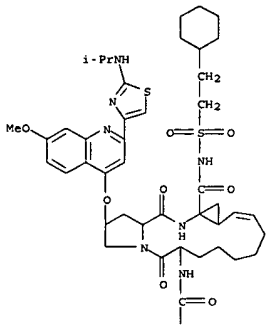
PAGE 2-B

RN 681145-38-0 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-14a-[[[(2-

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

cyclohexylethyl)sulfonyl]amino]carbonyl]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7 methoxy-2-[2-[(1 methylethyl)amino] 4 thiazolyl]-4-quinolinyl]oxy]-5,16-dioxocyclopropa[e]pyrrolo[1,2 a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

PAGE 1 A



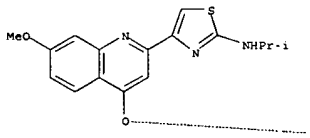
PAGE 2-A

RN 681145-39-1 CAPLUS
CN Carbamic acid,
[(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-14a-[[[(trichloromethyl)sulfonyl]amino]carbonyl]cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-,

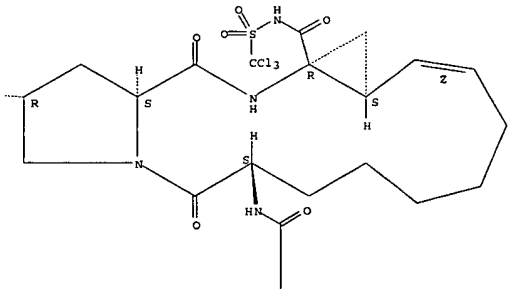
L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
cyclopentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



PAGE 2-B

RN 681145-40-4 CAPLUS
CN Carbamic acid,
[(2R,6S,12Z,13aS,14aR,16aS)-1,2,3,5,6,7,8,9,10,11,13a,14,14

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1 methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxo-14a-[[[(trifluoromethyl)sulfonyl]amino]carbonyl]cyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

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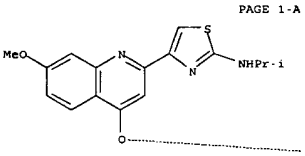
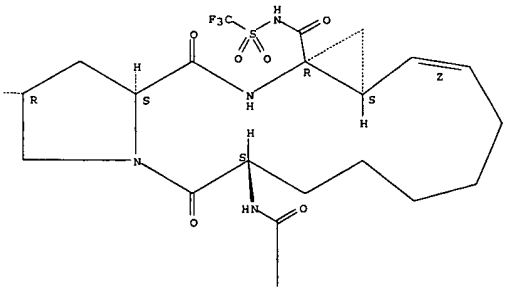


PAGE 1-B



L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

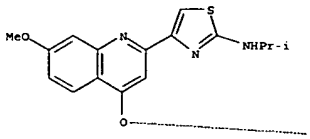
PAGE 2-B

RN 681145-41-5 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-14a-[[[(2-

fluorophenyl)sulfonyl]amino]carbonyl]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

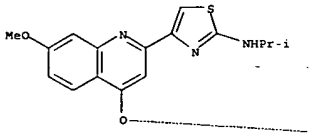
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

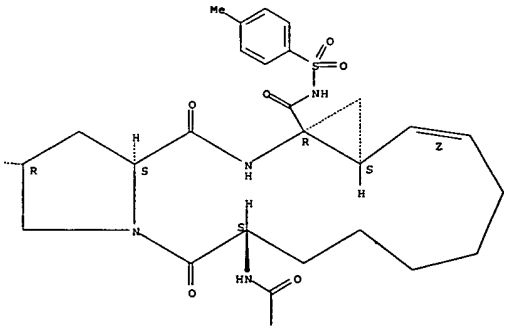


L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-A



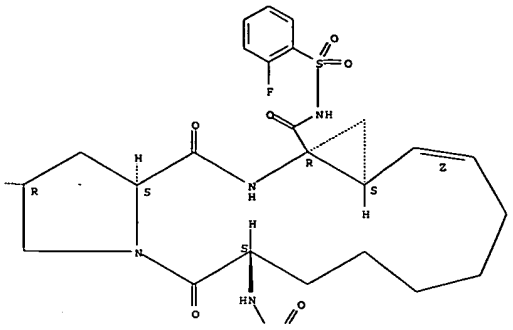
PAGE 1-B



PAGE 2-B

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-B



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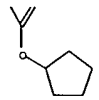

RN 681145-42-6 CAPLUS
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thiazolyl]-4-quinolinyl]oxy]-14a-[[[(4-methylphenyl)sulfonyl]amino]carbonyl]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:511084 CAPLUS
DOCUMENT NUMBER: 139:69527
TITLE: Preparation of macrocyclic compounds as inhibitors of hepatitis C virus
INVENTOR(S): Campbell, Jeffrey Allen; Good, Andrew Charles
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 225 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003053349	A2	20030703	WO 2002-US39926	20021213
WO 2003053349	A3	20040115		
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2004038872	A1	20040226	US 2002-317451	20021212
US 6867185	B2	20050315		
EP 1455809	A2	20040915	EP 2002-795860	20021213
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PRIORITY APPLN. INFO.:			US 2001-344080P	P 20011220
			US 2002-382103P	P 20020520
			WO 2002-US39926	W 20021213

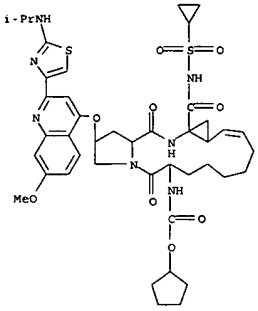
OTHER SOURCE(S): MARPAT 139:69527
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to macrocyclic compds. I [R1 = (cyclo)alkyl; R2 = H,
halo, alkyl, alkoxy, cycloalkoxy, (un)substituted aryl or heterocyclyl; R3
= H, halo, CF3, alkoxy, cycloalkoxy; R4 = NH2 or NHR6, where R6 is alkanoyl, alkylaminocarbonyl, or carbalkoxy; Q is a 3-9 atom (un)saturated
alkylene chain optionally containing 1-3 heteroatoms O, S, SO, or SO2], including methods for their synthesis and use in pharmaceutical compns. for therapeutic or prophylactic prevention or treatment of hepatitis C virus (HCV) infection. Thus,
3,13-diazatricyclo[11.3.0.04,6]hexadec-7-ene
derivative II was prepared by a multistep procedure and assayed for inhibition

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
of HCV NS3/4A protease (IC50 < 5 μM).
IT **552335-24-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of macrocyclic compds. as inhibitors of hepatitis C virus)
RN 552335-24-7 CAPLUS
CN Carbamic acid, [(2R,6S,12Z,13aS,14aR,16aS)-14a-

[[(cyclopropylsulfonyl)amino]carbonyl]-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-quinolinyl]oxy]-5,16-dioxocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecin-6-yl]-, cyclopentyl ester (9CI) (CA INDEX NAME)



COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	15.27	179.82
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.19	-2.19

FILE 'CAOLD' ENTERED AT 15:15:00 ON 04 APR 2005

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

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This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

L5 0 L3

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=> fil medl,biosis,embase,hcapl;s macrocyclic and hepatitis c
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     1.29     181.11

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -2.19

FILE 'MEDLINE' ENTERED AT 15:16:35 ON 04 APR 2005

FILE 'BIOSIS' ENTERED AT 15:16:35 ON 04 APR 2005
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FILE 'EMBASE' ENTERED AT 15:16:35 ON 04 APR 2005
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FILE 'HCAPLUS' ENTERED AT 15:16:35 ON 04 APR 2005
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L6           16 FILE MEDLINE
L7            5 FILE BIOSIS
L8            8 FILE EMBASE
L9           29 FILE HCAPLUS

TOTAL FOR ALL FILES
L10          58 MACROCYCLIC AND HEPATITIS C

=> s l10 not l4
L11          16 FILE MEDLINE
L12           5 FILE BIOSIS
L13           8 FILE EMBASE
L14          26 FILE HCAPLUS

TOTAL FOR ALL FILES
L15          55 L10 NOT L4

=> s llinas brunet m?/au;s bailey m?/au
L16          20 FILE MEDLINE
L17          50 FILE BIOSIS
L18          22 FILE EMBASE
L19          61 FILE HCAPLUS

TOTAL FOR ALL FILES
L20         153 LLINAS BRUNET M?/AU


L21         743 FILE MEDLINE
L22         936 FILE BIOSIS
L23         677 FILE EMBASE
L24        1056 FILE HCAPLUS

TOTAL FOR ALL FILES
L25        3412 BAILEY M?/AU
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Prepared by: Mary Hale @2-2507 Rem Bldg 1D86

```
=> s l20 and l25
L26           9 FILE MEDLINE
L27          22 FILE BIOSIS
L28           9 FILE EMBASE
L29          24 FILE HCAPLUS

TOTAL FOR ALL FILES
L30          64 L20 AND L25

=> s l15 and l30
L31           2 FILE MEDLINE
L32           1 FILE BIOSIS
L33           1 FILE EMBASE
L34           3 FILE HCAPLUS

TOTAL FOR ALL FILES
L35           7 L15 AND L30

=> s l35 not l4
L36           2 FILE MEDLINE
L37           1 FILE BIOSIS
L38           1 FILE EMBASE
L39           3 FILE HCAPLUS

TOTAL FOR ALL FILES
L40           7 L35 NOT L4

=> dup rem l40
PROCESSING COMPLETED FOR L40
L41            4 DUP REM L40 (3 DUPLICATES REMOVED)

=> d ibib abs 1-4 hitstr
```

L41 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:283507 HCAPLUS
TITLE: **Macrocyclic peptides active against the hepatitis c virus**
INVENTOR(S): **Llinas-Brunet, Montse; Bailey, Murray**; Bhardwaj, Punit; Forgione, Pasquale; Ghiro, Elise; Goudreau, Nathalie; Halmos, Teddy; Rancourt, Jean
PATENT ASSIGNEE(S): Boehringer Ingelheim International Gmbh, Germany; Boehringer Ingelheim Pharma Gmbh & Co Kg
SOURCE: PCT Int. Appl.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

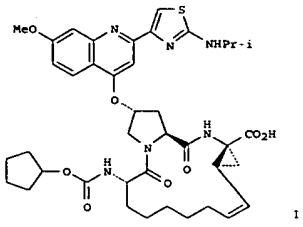
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005028501	A1	20050331	WO 2004-CA1658	20040920

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-504839P P 20030922

AB Compounds of formula I: wherein D, R4, R3, L0, L1, L2, R2 and RC are defined herein; or a pharmaceutically acceptable salt thereof, useful as inhibitors of the HCV NS3 protease.

L41 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:580783 HCAPLUS
DOCUMENT NUMBER: 141:261053
TITLE: Synthesis of BILN 2061, an HCV NS3 Protease Inhibitor with Proven Antiviral Effect in Humans
AUTHOR(S): Faucher, Anne-Marie; **Bailey, Murray D.**; Beaulieu, Pierre L.; Brochu, Christian; Duceppe, Jean-Simon; Ferland, Jean-Marie; Ghiro, Elise; Gorys, Vida; Halmos, Ted; Kawai, Stephen H.; Poirier, Martin; Simoneau, Bruno; Tsantrizos, Youla S.; **Llinas-Brunet, Montse**
CORPORATE SOURCE: Chemistry Department, Boehringer Ingelheim (Canada) Ltd., Laval, QC, H7S 2G5, Can.
SOURCE: Organic Letters (2004), 6(17), 2901-2904
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The synthesis of BILN 2061 (I), a **hepatitis C** virus (HCV) NS3 protease inhibitor with proven antiviral effect in humans, was accomplished in a convergent manner from four building blocks. The procedure described here was suitable for the preparation of multigram quantities of BILN 2061 for preclin. pharmacol. evaluation.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004136025 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15027850
TITLE: Structure-activity study on a novel series of **macrocyclic** inhibitors of the **hepatitis C** virus NS3 protease leading to the discovery of BILN 2061.
AUTHOR: **Llinas-Brunet Montse; Bailey Murray D**; Bolger Gordon; Brochu Christian; Faucher Anne-Marie; Ferland Jean Marie; Garneau Michel; Ghiro Elise; Gorys Vida; Grand-Maitre Chantal; Halmos Ted; Lapeyre-Paquette Nicole; Liard Francine; Poirier Martin; Rheaume Manon; Tsantrizos Youla S; Lamarre Daniel
CORPORATE SOURCE: Department of Chemistry, Boehringer Ingelheim (Canada) Ltd., 2100 Cunard Street, Laval, Quebec H7S 2G5, Canada.. mllinas@lav.boehringer-ingelheim.com
SOURCE: Journal of medicinal chemistry, (2004 Mar 25) 47 (7) 1605-8.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040319
Last Updated on STN: 20040511
Entered Medline: 20040510

AB From the discovery of competitive hexapeptide inhibitors, potent and selective HCV NS3 protease **macrocyclic** inhibitors have been identified. Structure-activity relationship studies were performed focusing on optimizing the N-terminal carbamate and the aromatic substituent on the (4R)-hydroxyproline moiety. Inhibitors meeting the potency criteria in the cell-based assay and with improved oral bioavailability in rats were identified. BILN 2061 was selected as the best compound, the first NS3 protease inhibitor reported with antiviral activity in man.

L41 ANSWER 4 OF 4 MEDLINE on STN
ACCESSION NUMBER: 2003541303 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14578911
TITLE: An NS3 protease inhibitor with antiviral effects in humans infected with **hepatitis C** virus.
COMMENT: Comment in: Gastroenterology. 2004 May;126(5):1487-8. PubMed ID: 15131814
Comment in: Nature. 2003 Nov 13;426(6963):129-31. PubMed ID: 14578912
Erratum in: Nature. 2003 Nov 20;246
AUTHOR: Lamarre Daniel; Anderson Paul C; **Bailey Murray**; Beaulieu Pierre; Bolger Gordon; Bonneau Pierre; Bos Michael; Cameron Dale R; Cartier Mireille; Cordingley Michael G; Faucher Anne-Marie; Goudreau Nathalie; Kawai Stephen H; Kukolj George; Lagace Lisette; LaPlante Steven R; Narjes Hans; Poupart Marc-Andre; Rancourt Jean; Sentjens Roel E; St George Roger; Simoneau Bruno; Steinmann Gerhard; Thibeault Diane; Tsantrizos Youla S; Weldon Steven M; Yong Chan-Loi; **Llinas-Brunet Montse**
CORPORATE SOURCE: Department of Biological Sciences Boehringer Ingelheim (Canada) Ltd, Laval, Quebec, H7S 2G5, Canada.. dlamarre@lav.boehringer-ingelheim.com
SOURCE: Nature, (2003 Nov 13) 426 (6963) 186-9. Electronic Publication: 2003-10-26.
Journal code: 0410462. ISSN: 1476-4687.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031119
Last Updated on STN: 20031216
Entered Medline: 20031215

AB **Hepatitis C** virus (HCV) infection is a serious cause of chronic liver disease worldwide with more than 170 million infected individuals at risk of developing significant morbidity and mortality. Current interferon-based therapies are suboptimal especially in patients infected with HCV genotype 1, and they are poorly tolerated, highlighting the unmet medical need for new therapeutics. The HCV-encoded NS3 protease is essential for viral replication and has long been considered an attractive target for therapeutic intervention in HCV-infected patients. Here we identify a class of specific and potent NS3 protease inhibitors and report the evaluation of BILN 2061, a small molecule inhibitor biologically available through oral ingestion and the first of its class in human trials. Administration of BILN 2061 to patients infected with HCV genotype 1 for 2 days resulted in an impressive reduction of HCV RNA plasma levels, and established proof-of-concept in humans for an HCV NS3 protease inhibitor. Our results further illustrate the potential of the viral-enzyme-targeted drug discovery approach for the development of new HCV therapeutics.

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=> s l15 not l35
L42          14 FILE MEDLINE
L43           4 FILE BIOSIS
L44           7 FILE EMBASE
L45          23 FILE HCAPLUS

TOTAL FOR ALL FILES
L46          48 L15 NOT L35

=> dup rem l46
PROCESSING COMPLETED FOR L46
L47           39 DUP REM L46 (9 DUPLICATES REMOVED)

=> d 1-39 ibib abs hitstr
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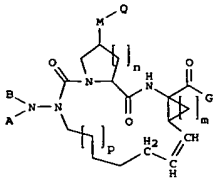
L47 ANSWER 1 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:99522 HCAPLUS
DOCUMENT NUMBER: 142:198355
TITLE: Preparation of aza-peptide macrocyclic hepatitis C serine protease inhibitors
INVENTOR(S): Wu, Frank X. H.; Nakajima, Suanne; Or, Yat Sun; Lu, Zhi-hui; Sun, Ying; Miao, Zhenwei; Wang, Zhe
PATENT ASSIGNEE(S): Enanta Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005010029	A1	20050203	WO 2004-US15802	20040519
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005065073	A1	20050324	US 2003-613206	20030703

PRIORITY APPLN. INFO.: US 2003-613206 A 20030703

GI



I

AB The invention relates to macrocyclic compds. I [A is H, CO2H or an ester, acyl, (thio)carbamoyl or sulfonyl groups; B is H or alkyl; G is

L47 ANSWER 1 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
OH, alkoxy, amino, sulfonyl, acyl or carbamoyl groups; M is absent, O, S, NH or substituted imino; Q is (un)substituted aryl, heteroaryl or heterocycloalkyl; m, n = 0-2; p = 0-4] or their pharmaceutically-acceptable salts, esters or prodrugs which inhibit serine protease activity, particularly the activity of hepatitis C virus (HCV) NS3-NS4A protease. The compds. of the invention interfere with the life cycle of the hepatitis C virus and are also useful as antiviral agents. Thus, compd. I (A = Me3CO2C, B = H, G = OEt, M-Q = OEt, m = n = p = 1; stereo not shown) was prepd. via N-acylation and cyclization reactions.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 2 OF 39 MEDLINE on STN
ACCESSION NUMBER: 2005103694 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15723328
TITLE: "Strong reasons make strong actions"--The antiviral efficacy of NS3/4A protease inhibitors.
AUTHOR: Lemon Stanley M; Yi Minkyung; Li Kui
CORPORATE SOURCE: Center for Hepatitis Research, Institute for Human Infections & Immunity, University of Texas Medical Branch, Galveston, TX, USA.
SOURCE: Hepatology (Baltimore, Md.), (2005 Mar) 41 (3) 671-4. Journal code: 8302946. ISSN: 0270-9139.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200503
ENTRY DATE: Entered STN: 20050301
Last Updated on STN: 20050318
Entered Medline: 20050317

L47 ANSWER 3 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:192430 HCAPLUS
TITLE: BILN2061 synthesis: Development of practical processes for the synthesis of the quinoline subunit and its coupling to the macrocyclic core
AUTHOR(S): Frutos, Rogelio P.; Beaulieu, Pierre; Farina, Vittorio; Johnson, Michael; Haddad, Nizar; Houpis, Ioannis; Yee, Nathan; Senanayake, Chris
CORPORATE SOURCE: Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT, 06877-0368, USA
SOURCE: Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, 2005 (2005), ORGN-410. American Chemical Society: Washington, D. C.
CODEN: 69GQMP
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB An integral part of our program to develop a practical, convergent and safe process for the synthesis of HCV (Hepatitis C Virus) protease inhibitor BILN2061 (1) was the development of suitable processes for the multi-kilogram preparation of its individual components, such as quinoline 3. Herein, we describe the development of an efficient, safe and practical process for the synthesis of 7-methoxy-2-(2-amino-4-thiazolyl)-quinoline (3) and its coupling to macrocycle (2). Our new process for the synthesis of 3 allowed for a more convergent approach to BILN2061 (1) and eliminated the use of potentially dangerous reagents such as diazomethane used in the Medicinal Chemical approach. Key aspects of the work described here are the optimization of the reaction conditions for the acetylation of m-anisidine via a Sugasawa reaction, as well as the optimization of the coupling of 2 and 3 by means of a brosylate displacement. Development of a process for the efficient synthesis of 3 allowed for the subsequent preparation of BILN2061 (1) in multi-kilogram amts. for toxicol., formulation and clin. studies.

L47 ANSWER 4 OF 39 MEDLINE on STN
ACCESSION NUMBER: 2004547753 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15521029
TITLE: **Hepatitis C**: it's a long way to new therapy, it's a long way to go...
COMMENT: Comment on: Gastroenterology. 2004 Nov;127(5):1347-55.
PubMed ID: 15521004
AUTHOR: Pawlotsky Jean-Michel
SOURCE: Gastroenterology, (2004 Nov) 127 (5) 1629-32.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200412
ENTRY DATE: Entered STN: 20041103
Last Updated on STN: 20041220
Entered Medline: 20041203

L47 ANSWER 5 OF 39 MEDLINE on STN
ACCESSION NUMBER: 2004184110 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15080102
TITLE: **Hepatitis C** drug being developed.
AUTHOR: Anonymous
SOURCE: AIDS patient care and STDs, (2004 Jan) 18 (1) 62.
Journal code: 9607225. ISSN: 1087-2914.
PUB. COUNTRY: United States
DOCUMENT TYPE: News Announcement
LANGUAGE: English
FILE SEGMENT: AIDS
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040415
Last Updated on STN: 20040501
Entered Medline: 20040430

L47 ANSWER 6 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:927230 HCAPLUS
DOCUMENT NUMBER: 141:395807
TITLE: Preparation of **macrocyclic** isoquinoline peptide inhibitors of **hepatitis C** virus
INVENTOR(S): McPhee, Fiona; Campbell, Jeffrey Allen; Li, Wenying; D'Andrea, Stanley; Zheng, Zhizhen Barbara; Good, Andrew Charles; Carini, David J.; Johnson, Barry L.; Scola, Paul Michael
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 280 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004094452	A2	20041104	WO 2004-US11824	20040416
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2003-463423P P 20030416

OTHER SOURCE(S): MARPAT 141:395807
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention discloses **macrocyclic** isoquinoline peptides I [R1-R6 are independently H, alkyl, cycloalkyl, alkoxy, cyano, halo, hydroxy, alkanoyl, nitro, amino, carboxyl, alkylsulfonyl, etc.; R7 is NH2 or NR10R11, where R10 is alkyl, haloalkyl, carbamoyl, carboxy or thiocarboxy ester or an acyl group; R11 is H, alkyl or haloalkyl; R8, R9 are H or alkyl optionally substituted with halogen, alkoxy or haloalkoxy; Q is a saturated or unsatd. chain optionally containing one to three heteroatoms O, S(O)0-2, NH, alkylimino, cycloalkylimino, etc.; W is OH, NHS(O)1-2R12, where R12 is alkyl, cycloalkyl, aryl or heterocyclyl] or their pharmaceutically-acceptable enantiomers, diastereomers, salts, solvates or prodrugs and methods for using them to inhibit the **hepatitis C** virus (HCV). Thus, cyclic peptide II (Boc = tert-butoxycarbonyl) was prepared via peptide coupling and olefin metathesis cyclization reactions and showed IC50 and EC50 values <0.05 μM in the HCV NS3/4A protease inhibition assay. Combination studies showed that

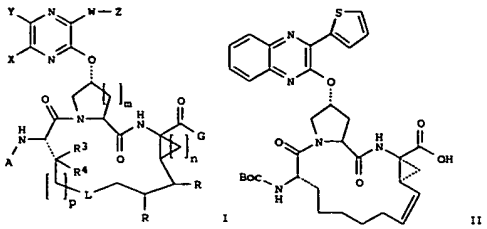
L47 ANSWER 6 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
treatment of replicon cells with an HCV NS3 protease inhibitor, compd. II and Intron A and/or inhibitors targeting HCV NS5A and/or NS5B, yield additive to synergistic antiviral effects.

L47 ANSWER 7 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:927005 HCAPLUS
DOCUMENT NUMBER: 141:395806
TITLE: Preparation of quinoxalinyl **macrocyclic** **hepatitis C** serine protease inhibitors
INVENTOR(S): Nakajima, Suanne; Sun, Ying; Tang, Datong; Xu, Gouyou; Porter, Brian; Or, Yat Sun; Wang, Zhe; Miao, Zhenwei
PATENT ASSIGNEE(S): Enanta Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004093798	A2	20041104	WO 2004-US11841	20040416
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004266668	A1	20041230	US 2004-826743	20040416
PRIORITY APPLN. INFO.:			US 2003-418759 P	20030418
			US 2003-509071P P	20030418

OTHER SOURCE(S): MARPAT 141:395806
GI

L47 ANSWER 7 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I II

AB The invention relates to **macrocyclic** compds. I [A is H, CO2R1, COR2, CONHR2, CSNHR2 or SO2R2; G is OH, alkoxy, NHSO2R1, COR2, CO2R1 or CONHR2; L is S, SCH2, SO2, O, COCH2, CHMeCH2, etc.; m, n = 0-2; p = 0-4; R2 is a bond or H2; R1 is H, (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl,heteroaryl, heteroarylalkyl or heterocycloalkyl; R2 is any group given for R1 or mono- or dialkylamino or -arylamino; R3, R4 not defined; X and Y taken together with the carbon atoms to which they are attached form (un)substituted aryl or heteroaryl; W is absent, O, S, NH, C(O)NR1 or NR1; Z is H, -CN, -SCN, -NCO, -NCS, NHNH2, N3, halo, cycloalkyl, aryl, etc.] or their pharmaceutically-acceptable salts, esters or prodrugs which inhibit serine protease activity, particularly the activity of **hepatitis C** virus (HCV) NS3-NS4A protease. The compds. of the invention interfere with the life cycle of the **hepatitis C** virus and are also useful as antiviral agents. Thus, macrocycle II (Boc = tert-butoxycarbonyl) was prepared via peptide coupling and ring-closing metathesis reactions.

L47 ANSWER 8 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:905774 HCAPLUS
DOCUMENT NUMBER: 141:380136
TITLE: Process for preparing **macrocyclic** compounds
INVENTOR(S): Donsbach, Kai; Ecker, Dieter; Frutos, Rogelio Perez; Gallou, Fabrice; Gutheil, Dieter; Haddad, Nizar; Hagenkoetter, Robert; Kemmer, Dirk; Kroeber, Jutta; Nicola, Thomas; Schnaubelt, Juergen; Schul, Michael; Simpson, Robert Donald; Wei, Xudong; Winter, Eric; Xu, Yibo; Yee, Nathan K.; Brandenburg, Joerg
PATENT ASSIGNEE(S): Boehringer Ingelheim International, G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004092203	A2	20041028	WO 2004-US10476	20040406
WO 2004092203	A3	20041209		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005049187	A1	20050303	US 2004-818657	20040406
PRIORITY APPLN. INFO.:			US 2003-461662P P	20030410

OTHER SOURCE(S): MARPAT 141:380136
GI

L47 ANSWER 8 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

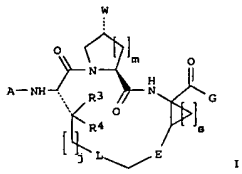
AB Disclosed is a process for preparing **macrocyclic** compds. I [W is CH or N; R1 is H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy or an amino group; R2 is H, halo, alkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, (un)substituted cycloalkyl, aryl or heterocyclyl; R3 is OH, NH2, aryl-, heteroaryl- or acylamino; D is alkylene which may be substituted by R4 (alkyl, alkoxy, halo, amino, etc.); A is CO2H or an amide or salt] which are potent active agents for the treatment of **hepatitis C** virus (HCV) infection. The process involves reaction of a 4-hydroxyproline sulfonate macrocycle with a 4-naphthol or 4-quinolinol derivative and was applied to the synthesis of II by a multistep sequence.

L47 ANSWER 9 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:698218 HCAPLUS
DOCUMENT NUMBER: 141:220883
TITLE: **Macrocyclic hepatitis C** virus (HCV) serine protease NS3 inhibitors, their synthesis and use to prevent HCV infection
INVENTOR(S): Miao, Zenwei; Sun, Ying; Wu, Frank; Nakajima, Suanne; Xu, Guoyou; Or, Yat Sun; Wang, Zhe
PATENT ASSIGNEE(S): Enanta Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 299 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004072243	A2	20040826	WO 2004 US3479	20040206
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004180815	A1	20040916	US 2003-384120	20030307
PRIORITY APPLN. INFO.:			US 2003-360947 A	20030207
			US 2003-365854 A	20030213
			US 2003-384120 A	20030307

OTHER SOURCE(S): MARPAT 141:220883
GI

L47 ANSWER 9 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I

AB The present invention relates to compds. I [A = H, COR2, COOR1, CONHR2, etc.; G = OH, COR2, COOR1, CONHR1, etc.; L = S, SO2, O, COCH2, CF2CH2, etc.; j = 0-4; m, s = 0-2; R1,R2 = H, C1-6-alkyl, (substituted)aryl, heteroaryl, etc.; R3,R4 = H, OH, Me, CN, SH, halo, NO2, NH2, amide, MeO, CF3O, CF3; E = CH:CH, CH2CH2; W = (un)substituted heterocyclic ring], or a pharmaceutically acceptable salt, ester, or prodrug thereof, and to methods for their synthesis. The compds. inhibit serine protease activity, particularly the activity of HCV NS3-NS4A protease. Consequently, the compds. of the present invention interfere with the life cycle of HCV and are also useful as antiviral agents. The present invention further relates to pharmaceutical compns. comprising the aforementioned compds. for administration to a subject suffering from HCV infection. The invention also relates to methods of treating an HCV infection in a subject by administering a pharmaceutical composition comprising the compds. of the present invention.

L47 ANSWER 10 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:177944 HCAPLUS
DOCUMENT NUMBER: 140:235737
TITLE: Production of **macrocyclic** pyrimidine derivatives and their use as drugs
INVENTOR(S): Luecking, Ulrich; Siemeister, Gerhard; Schaefer, Martina; Briem, Hans
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 42 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10239042	A1	20040304	DE 2002-10239042	20020821
WO 2004026881	A1	20040401	WO 2003-EP8664	20030805
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004209895	A1	20041021	US 2003-644076	20030820
PRIORITY APPLN. INFO.:			DE 2002-10239042 A	20020821
			US 2002-413444P P	20020926

OTHER SOURCE(S): CASREACT 140:235737; MARPAT 140:235737
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB **Macrocyclic** pyrimidine derivs., e.g., I [R1, R5 = H, OH, halogen, NO2, CN, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, etc.; R2 = H, C1-10-alkyl; R3 = H, halogen, NO2, CN, C1-10-alkyl, C1-10-haloalkyl, C2-10-alkenyl, C2-10-alkynyl, C2-10-cycloalkyl, OH, C1-6-alkoxy, C1-6-alkylthio, NH2, NH(CH2)p-C3-10-cycloalkyl, C1-6-hydroxyalkyl, (C1-6-alkoxy)-(C1-6-alkyl), NH(C1-6-alkyl), N(C1-6-alkyl)2, SO(C1-6-alkyl), SO2(C1-6-alkyl), (C1-6-alkanoyl), CONR8R9, COR10, (C1-6-alkyl)-OAc, CO2H, aryl, heteroaryl, etc.; R4 = H, halogen, C1-4-alkyl; R6, R7, R8, R9, R10, R11 = H, OH, halogen, C1-12-alkoxy, C1-6-alkylthio, NH2, CN, C1-6-alkyl, NH(CH2)p-C3-10-cycloalkyl, C3-10-cycloalkyl, C1-6-hydroxyalkyl, C2-6-alkenyl, C2-6-alkynyl, NH-(C1-6-alkyl), N(C1-6-alkyl)2, SO(C1-6-alkyl), SO2(C1-6-alkyl), C1-6-alkanoyl, CONR8R9, etc.; X, Y = O, S, NR11, NR11O, ONR11, CR6R7, C:O, C:S, SO, SO2, C(:O)O, OC(:O), S(:O)O, OS(:O), SO2-O, O-SO2, CONR8, NR8CO, OC(:O)NR8, NR8C(:O)O, CSNR8, NR8CS, OC(:S)NR8, SONR8, NR8SO, SO2NR8, NR8SO2, NR8COR9, NR8CSNR9, NR8SONR9, NR8SO2NR9, NR8CONR9, NR8CSNR9; A =

L47 ANSWER 10 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
aryl, heteroaryl; B = bond ; m = 0 - 8; n, p = 0 - 6], II (D = NH2, NO2) and III (U = OH), their isomers, stereoisomers, enantiomers and their salts, which are inhibitors of the cyclin-dependent kinases, procedures for their prodn. as well as their use as medicine for the treatment of different illnesses is described. Prepn. of I is characterized by macrocyclization of pyrimidine IV (L = leaving group) in the presence of an acid and is itself prepd. via redn. of nitro compd. V (L = leaving group). Thus, I [R1 = R2 = R4 = R5 = H, R3 = Br, A = 1,3-phenylene, (Y)nB(X)n = NH(CH2)5NHSO2, m = n = 1] was prepd. via macrocyclization of IV [L = Cl, R1 = R2 = R4 = R5 = H, R3 = Br, A = 1,3-phenylene, (Y)nB(X)n = NH(CH2)5NHSO2, m = n = 1]. The inhibitory activity of I [R1 = R2 = R4 = R5 = H, R3 = Br, A = 1,3-phenylene, (Y)nB(X)n = NH(CH2)5NHSO2, m = n = 1] towards cyclin-dependent kinases was detd. [IC50 = 420 nM vs. CDK1/CycB, IC50 = 200 nM vs. CDK2/CycE, IC50 = 1.1 nM vs. MCF7].

L47 ANSWER 11 OF 39 MEDLINE on STN
ACCESSION NUMBER: 2004197103 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14766754
TITLE: In vitro resistance studies of **hepatitis** C virus serine protease inhibitors, VX-950 and BILN 2061: structural analysis indicates different resistance mechanisms.
AUTHOR: Lin Chao; Lin Kai; Luong Yu-Ping; Rao B Govinda; Wei Yun-Yi; Brennan Debra L; Fulghum John R; Hsiao Hsun-Mei; Ma Sue; Maxwell John P; Cottrell Kevin M; Perni Robert B; Gates Cynthia A; Kwong Ann D
CORPORATE SOURCE: Vertex Pharmaceuticals Inc., Cambridge, Massachusetts 02139, USA.. chao_lin@vrtx.com
SOURCE: Journal of biological chemistry, (2004 Apr 23) 279 (17) 17508-14. Electronic Publication: 2004-02-06. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20040420
Last Updated on STN: 20040611
Entered Medline: 20040610

AB We have used a structure-based drug design approach to identify small molecule inhibitors of the **hepatitis** C virus (HCV) NS3.4A protease as potential candidates for new anti-HCV therapies. VX-950 is a potent NS3.4A protease inhibitor that was recently selected as a clinical development candidate for **hepatitis** C treatment. In this report, we describe in vitro resistance studies using a subgenomic replicon system to compare VX-950 with another HCV NS3.4A protease inhibitor, BILN 2061, for which the Phase I clinical trial results were reported recently. Distinct drug-resistant substitutions of a single amino acid were identified in the HCV NS3 serine protease domain for both inhibitors. The resistance conferred by these mutations was confirmed by characterization of the mutant enzymes and replicon cells that contain the single amino acid substitutions. The major BILN 2061-resistant mutations at Asp(168) are fully susceptible to VX-950, and the dominant resistant mutation against VX-950 at Ala(156) remains sensitive to BILN 2061. Modeling analysis suggests that there are different mechanisms of resistance to VX-950 and BILN 2061.

L47 ANSWER 12 OF 39 MEDLINE on STN
ACCESSION NUMBER: 2004319426 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15220408
TITLE: Sensitivity of NS3 serine proteases from **hepatitis** C virus genotypes 2 and 3 to the inhibitor BILN 2061.
AUTHOR: Thibeault Diane; Bousquet Christiane; Gingras Rock; Lagace Lisette; Maurice Roger; White Peter W; Lamarre Daniel
CORPORATE SOURCE: Department of Biological Sciences, Boehringer Ingelheim (Canada) Ltd, Research and Development, Laval, Quebec H7S 2G5, Canada.. dthibeault@lav.boehringer-ingelheim.com
SOURCE: Journal of virology, (2004 Jul) 78 (14) 7352-9. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 20040629
Last Updated on STN: 20040804
Entered Medline: 20040803

AB **Hepatitis** C virus (HCV) displays a high degree of genetic variability. Six genotypes and more than 50 subtypes have been identified to date. In this report, kinetic profiles were determined for NS3 proteases of genotypes 1a, 1b, 2ac, 2b, and 3a, revealing no major differences in activity. In vitro sensitivity studies with BILN 2061 showed a decrease in affinity for proteases of genotypes 2 and 3 (K(i), 80 to 90 nM) compared to genotype 1 enzymes (K(i), 1.5 nM). To understand the reduced sensitivity of genotypes 2 and 3 to BILN 2061, active-site residues in the proximity of the inhibitor binding site were replaced in the genotype-1b enzyme with the corresponding genotype-2b or -3a residues. The replacement of five residues at positions 78, 79, 80, 122, and 132 accounted for most of the reduced sensitivity of genotype 2b, while replacement of residue 168 alone could account for the reduced sensitivity of genotype 3a. BILN 2061 remains a potent inhibitor of these non-genotype-1 NS3-NS4A proteins, with K(i) values below 100 nM. This in vitro potency, in conjunction with the good pharmacokinetic data reported for humans, suggests that there is potential for BILN 2061 as an antiviral agent for individuals infected with non-genotype-1 HCV.

L47 ANSWER 13 OF 39 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004450606 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15357576
TITLE: Potent inhibitors of the **hepatitis** C virus NS3 protease: design and synthesis of **macrocyclic** substrate-based beta-strand mimics.
AUTHOR: Goudreau Nathalie; Brochu Christian; Cameron Dale R; Duceppe Jean-Simon; Faucher Anne-Marie; Ferland Jean-Marie; Grand-Maitre Chantal; Poirier Martin; Simoneau Bruno; Tsantrizos Youla S
CORPORATE SOURCE: Department of Chemistry, Boehringer Ingelheim Ltd., Research and Development, 2100 Cunard Street, Laval, Quebec, Canada H7S 2G5.
SOURCE: Journal of organic chemistry, (2004 Sep 17) 69 (19) 6185-201. Journal code: 2985193R. ISSN: 0022-3263.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20040911
Last Updated on STN: 20041219

AB The virally encoded NS3 protease is essential to the life cycle of the **hepatitis** C virus (HCV), an important human pathogen causing chronic hepatitis, cirrhosis of the liver, and hepatocellular carcinoma. The design and synthesis of 15-membered ring beta-strand mimics which are capable of inhibiting the interactions between the HCV NS3 protease enzyme and its polyprotein substrate will be described. The binding interactions between a **macrocyclic** ligand and the enzyme were explored by NMR and molecular dynamics, and a model of the ligand/enzyme complex was developed.

L47 ANSWER 14 OF 39 MEDLINE on STN
ACCESSION NUMBER: 2004256486 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15155230
TITLE: Mutations conferring resistance to a potent **hepatitis** C virus serine protease inhibitor in vitro.
AUTHOR: Lu Liangjun; Pilot-Matias Tami J; Stewart Kent D; Randolph John T; Pithawalla Ron; He Wenping; Huang Peggy P; Klein Larry L; Mo Hongmei; Molla Akhteruzzaman
CORPORATE SOURCE: Antiviral Research, Abbott Laboratories, Global Pharmaceutical Research and Development, Abbott Park, IL 60064-6217, USA.. liangjun.lu@abbott.com
SOURCE: Antimicrobial agents and chemotherapy, (2004 Jun) 48 (6) 2260-6. Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 20040525
Last Updated on STN: 20040714
Entered Medline: 20040713

AB BILN 2061 is a novel, specific **hepatitis** C virus (HCV) NS3 serine protease inhibitor discovered by Boehringer Ingelheim that has shown potent activity against HCV replicons in tissue culture and is currently under clinical investigation for the treatment of HCV infection. The poor fidelity of the HCV RNA-dependent RNA polymerase will likely lead to the development of drug-resistant viruses in treated patients. The development of resistance to BILN 2061 was studied by the in vitro passage of HCV genotype 1b replicon cells in the presence of a fixed concentration of the drug. Three weeks posttreatment, four colonies were expanded for genotypic and phenotypic characterization. The 50% inhibitory concentrations of BILN 2061 for these colonies were 72- to 1,228-fold higher than that for the wild-type replicon. Sequencing of the individual colonies identified several mutations in the NS3 serine protease gene. Molecular clones containing the single amino acid substitution A156T, R155Q, or D168V resulted in 357-fold, 24-fold, and 144-fold reductions in susceptibility to BILN 2061, respectively, compared to the level of susceptibility shown by the wild-type replicon. Modeling studies indicate that all three of these residues are located in close proximity to the inhibitor binding site. These findings, in addition to the three-dimensional structure analysis of the NS3/NS4A serine protease inhibitor complex, provide a strategic guide for the development of next-generation inhibitors of HCV NS3/NS4A serine protease.

L47 ANSWER 15 OF 39 MEDLINE on STN
ACCESSION NUMBER: 2004116220 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15006379
TITLE: Inhibitors of **hepatitis** C virus NS3.4A protease 2. Warhead SAR and optimization.
AUTHOR: Perni Robert B; Pitlik Janos; Britt Shawn D; Court John J; Courtney Lawrence F; Deininger David D; Farmer Luc J; Gates Cynthia A; Harbeson Scott L; Levin Rhonda B; Lin Chao; Lin Kai; Moon Young-Choon; Luong Yu-Ping; O'Malley Ethan T; Rao B Govinda; Thomson John A; Tung Roger D; Van Drie John H; Wei Yunyi
CORPORATE SOURCE: Vertex Pharmaceuticals Inc., 130 Waverly Street, Cambridge, MA 02139, USA.
SOURCE: Bioorganic & medicinal chemistry letters, (2004 Mar 22) 14 (6) 1441-6.
Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200410
ENTRY DATE: Entered STN: 20040310
Last Updated on STN: 20041029
Entered Medline: 20041028
AB The alpha-ketoamide warhead (e.g., 15) was found to be a practical replacement for aliphatic aldehydes in a series of HCV NS3.4A protease inhibitors. Structure-activity relationships and prime side optimization are discussed.

L47 ANSWER 16 OF 39 MEDLINE on STN
ACCESSION NUMBER: 2004547728 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15521004
TITLE: Short-term antiviral efficacy of BILN 2061, a **hepatitis** C virus serine protease inhibitor, in **hepatitis** C genotype 1 patients.
COMMENT: Comment in: Gastroenterology. 2004 Nov;127(5):1629-32.
PubMed ID: 15521029
AUTHOR: Hinrichsen Holger; Benhamou Yves; Wedemeyer Heiner; Reiser Markus; Sentjens Roel E; Calleja Jose L; Forns Xavier; Erhardt Andreas; Cronlein Jens; Chaves Ricardo L; Yong Chan-Loi; Nehmiz Gerhard; Steinmann Gerhard G
CORPORATE SOURCE: Medizinische Universitatsklinik, Kiel, Germany.. hhinrichsen31med.uni-kiel.de
SOURCE: Gastroenterology, (2004 Nov) 127 (5) 1347 55.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200412
ENTRY DATE: Entered STN: 20041103
Last Updated on STN: 20041220
Entered Medline: 20041203
AB BACKGROUND AND AIMS: Novel, potent, and well-tolerated **hepatitis** C virus (HCV) drugs are needed. BILN 2061 is a potent and specific inhibitor of HCV serine protease in vitro. Preclinical toxicology data and studies in healthy volunteers supported the administration of BILN 2061 to patients with HCV infection. METHODS: The antiviral efficacy, pharmacokinetics, and tolerability of 25, 200, and 500 mg BILN 2061 twice daily given as monotherapy for 2 days in 31 patients infected with chronic genotype 1 HCV infection and with minimal liver fibrosis (Ishak score of 0-2) were assessed in a placebo-controlled, double-blind pilot study. In 2 subsequent placebo-controlled studies of similar design, 200 mg BILN 2061 twice daily was administered for 2 days to 10 patients with advanced liver fibrosis (Ishak score of 3 or 4) and to 10 patients with compensated cirrhosis (Ishak score of 5 or 6). RESULTS: Viral RNA reductions of 2-3 log 10 copies/mL were achieved in most of the patients. There was a trend toward a higher number of patients receiving 500 mg BILN 2061 achieving a viral RNA reduction > or =3 log(10) copies/mL as compared with patients receiving 25 mg BILN 2061. Advanced fibrosis or compensated cirrhosis did not affect the antiviral efficacy of BILN 2061. BILN 2061 was well tolerated in all studies. CONCLUSIONS: BILN 2061 is a well-tolerated and very active compound that reduced serum viral RNA concentrations after 2 days of treatment in patients infected with genotype 1 HCV independent of the degree of fibrosis. Nevertheless, further clinical trials are on hold pending resolution of animal toxicity issues.

L47 ANSWER 16 OF 39 MEDLINE on STN (Continued)

L47 ANSWER 17 OF 39 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2004285867 EMBASE
TITLE: Inhibitors of HSP90 and other chaperones for the treatment of cancer.
AUTHOR: Dymock B.W.; Drysdale M.J.; McDonald E.; Workman P.
CORPORATE SOURCE: M.J. Drysdale, Vernalis Ltd., Granta Park, Cambridge CB1 6GB, United Kingdom
SOURCE: Expert Opinion on Therapeutic Patents, (2004) Vol. 14, No. 6, pp. 837-847.
Refs: 55
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
017 Public Health, Social Medicine and Epidemiology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040722
Last Updated on STN: 20040722
AB Molecular chaperones are proteins that ensure the appropriate folding, stability and function of other proteins in the cell. There is increasing evidence that molecular chaperones are not only important in normal cell homeostasis and response to stresses, such as heat shock, but can also be involved in disease pathology. In particular, HSP90 has emerged as an important potential drug target in oncology. This is because it is essential for the stability of a long list of 'client proteins', including ErbB2/human epithelial growth factor receptor (HER)2, Raf-1, Akt/protein kinase B (PKB), Polo-1, Met, mutant p53 and human telomerase reverse transcriptase (hTERT), as well as the oestrogen and androgen receptor. Inhibition of HSP90 leads to depletion of these oncogenic clients by the ubiquitin proteasome pathway, thereby providing a simultaneous combinatorial attack on all of the hallmark phenotypic traits of cancer cells. Because of the rapid progress made, this review focuses on the patents dealing with the discovery and application of small molecule inhibitors of HSP90, although limited coverage of other applications in the area of HSP90 and additional chaperones is also included. Pioneering work with natural products, namely geldanamycin and related ansamycin antibiotics together with radicicol macrocycle derivatives, established the therapeutic potential of inhibiting the essential N-terminal ATPase of HSP90 by competing at the nucleotide binding site. A geldanamycin analogue, 17-(desmethoxy), 17-allylamino geldanamycin (17AAG), is completing Phase I clinical trials with promising initial results. The use of high-throughput screening and rational design based on X-ray crystal structures of HSP90 has led to the discovery of small molecule HSP90 inhibitors based on purine and pyrazole scaffolds. The continued progression of these various compound classes into clinical trials should help to establish proof of concept for inhibition of HSP90 as a viable therapeutic approach for the treatment of cancer and potentially other diseases. This would in turn validate protein folding as a strategy for drug development and encourage additional chaperones to be explored as molecular targets. 2004 .COPYRGT. Ashley Publications Ltd.

L47 ANSWER 17 OF 39 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. (Continued)

L47 ANSWER 18 OF 39 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004507380 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15386268
TITLE: The design of a potent inhibitor of the **hepatitis** C virus NS3 protease: BILN 2061--from the NMR tube to the clinic.
AUTHOR: Tsantrizos Youla S
CORPORATE SOURCE: Boehringer Ingelheim (Canada) Ltd., Research and Development, 2100 Cunard Street, Laval (Quebec) H7S 2G5, Canada.. ytsantrizos@lav.boehringer-ingelheim.com
SOURCE: Biopolymers, (2004) 76 (4) 309-23.
Journal code: 0372525. ISSN: 0006-3525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 20041013
Last Updated on STN: 20041219
Entered Medline: 20041119

AB The virally encoded serine protease NS3/NS4A is essential to the life cycle of the **hepatitis** C virus (HCV), an important human pathogen causing chronic hepatitis, cirrhosis of the liver, and hepatocellular carcinoma. Until very recently, the design of inhibitors for the HCV NS3 protease was limited to large peptidomimetic compounds with poor pharmacokinetic properties, making drug discovery an extremely challenging endeavor. In our quest for the discovery of a small-molecule lead that could block replication of the **hepatitis** C virus by binding to the HCV NS3 protease, the critical protein-polypeptide interactions between the virally encoded NS3 serine protease and its polyprotein substrate were investigated. Lead optimization of a substrate-based hexapeptide, guided by structural data, led to the understanding of the molecular dynamics and electronic effects that modulate the affinity of peptidomimetic ligands for the active site of this enzyme. **Macrocyclic** beta-strand scaffolds were designed that allowed the discovery of potent, highly selective, and orally bioavailable compounds. These molecules were the first HCV NS3 protease inhibitors reported that inhibit replication of HCV subgenomic RNA in a cell-based replicon assay at low nanomolar concentrations. Optimization of their biopharmaceutical properties led to the discovery of the clinical candidate BILN 2061. Oral administration of BILN 2061 to patients infected with the **hepatitis** C genotype 1 virus resulted in an impressive reduction of viral RNA levels, establishing proof-of-concept for HCV NS3 protease inhibitors as therapeutic agents in humans.

L47 ANSWER 19 OF 39 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003612387 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14695562
TITLE: Solid-phase synthesis and screening of **macrocyclic** nucleotide-hybrid compounds targeted to **hepatitis** C NS5B.
AUTHOR: Smietana Michael; Johnson Robert B; Wang Q May; Kool Eric T
CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, CA 94305-5080, USA.
CONTRACT NUMBER: GM62658 (NIGMS)
RR15054 (NCRR)
SOURCE: Chemistry (Weinheim an der Bergstrasse, Germany), (2004 Jan 5) 10 (1) 173-81.
Journal code: 9513783. ISSN: 0947-6539.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20031230
Last Updated on STN: 20041001
Entered Medline: 20040930

AB A convergent strategy for the synthesis of cyclic nucleotide-hybrid molecules on controlled pore glass is reported. A major advantage of the approach is the lack of restrictions on the sequence and structural variation, allowing the incorporation of modified ribonucleosides (such as 2'-OMe-ribonucleotides), as well as threoninol derivatives. This methodology allows a fully automated assembly by means of standard phosphoramidite chemistry and is based on a recently published procedure for the preparation of cyclic oligodinucleotides in the DNA series (M. Smietana, E. T. Kool, Angew. Chemical 2002, 114, 3856-3859; Angew. Chemical Int. Ed. Engl. 2002, 41, 3704-3707). A library of potential cyclic hybrid inhibitor compounds targeting **hepatitis** C virus NS5B enzyme (the replicating polymerase of HCV) was generated by means of the parallel-pool strategy. Screening of the library revealed that cyclic hybrid c(C(OME)EthenodA) was a significant inhibitor of NS5B, with an IC(50) of 40 microM. Preliminary structure-activity studies of this lead compound are described.

L47 ANSWER 20 OF 39 MEDLINE on STN
ACCESSION NUMBER: 2004203536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14980127
TITLE: Review of recent research on **hepatitis** C therapy for 54th annual meeting of the American association for the study of liver diseases.
AUTHOR: Wei Lai
CORPORATE SOURCE: Hepatology Institute, Peking University People's Hospital, Beijing 100044, China.
SOURCE: Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chinese journal of hepatology, (2004 Feb) 12 (2) 118-20.
Journal code: 9710009. ISSN: 1007-3418.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20040423
Last Updated on STN: 20040528
Entered Medline: 20040527

L47 ANSWER 21 OF 39 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:383285 BIOSIS
DOCUMENT NUMBER: PREV200400382728
TITLE: HCV NS3 protease and NS5B polymerase inhibitors as antiviral agents.
AUTHOR(S): Beaulieu, P. L.
SOURCE: Antiviral Research, (May 2004) Vol. 62, No. 2, pp. A82. print.
Meeting Info.: Seventeenth International Conference on Antiviral Research. Tucson, AZ, USA. May 02-06, 2004. International Society for Antiviral Research.
ISSN: 0166-3542 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Sep 2004
Last Updated on STN: 29 Sep 2004

L47 ANSWER 22 OF 39 MEDLINE on STN

ACCESSION NUMBER: 2003541304 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14578912
TITLE: Virology: fresh assault on **hepatitis C**.
COMMENT: Comment on: Nature. 2003 Nov 13;426(6963):186-9. PubMed ID:
14578911
AUTHOR: Rice Charles M
SOURCE: Nature, (2003 Nov 13) 426 (6963) 129-31.
Journal code: 0410462. ISSN: 1476-4687.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Commentary
News Announcement
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031119
Last Updated on STN: 20031216
Entered Medline: 20031215

L47 ANSWER 23 OF 39 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 4

ACCESSION NUMBER: 2003:422134 BIOSIS
DOCUMENT NUMBER: PREV200300422134
TITLE: **Macrocyclic** peptides active against the **hepatitis C** virus.
AUTHOR(S): Tsantrizos, Youla S. [Inventor, Reprint Author]; Cameron, Dale R. [Inventor]; Faucher, Anne-Marie [Inventor]; Ghiro, Elise [Inventor]; Goudreau, Nathalie [Inventor]; Halmos, Teddy [Inventor]; Llinas-Brunet, Montse [Inventor]
CORPORATE SOURCE: Saint-Laurent, Canada
ASSIGNEE: Boehringer Ingelheim (Canada) Ltd, Laval, Canada
PATENT INFORMATION: US 6608027 August 19, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Aug 19 2003) Vol. 1273, No. 3. http://www.uspto.gov/web/menu/patdata.html. e-file.
ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Sep 2003
Last Updated on STN: 10 Sep 2003

AB The present invention covers **macrocyclic** compounds of formula I active in-vitro and in cellular assays against the NS3 protease of the **hepatitis C** virus. ##STR1## wherein W, R21, R22, R3, R4, D and A are as defined herein, or a pharmaceutically acceptable salts or ester thereof.

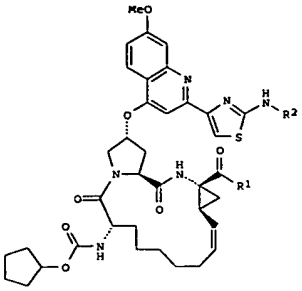
L47 ANSWER 24 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:610478 HCAPLUS
DOCUMENT NUMBER: 139:164979
TITLE: Preparation of **macrocyclic** peptides which are active against **hepatitis C** virus
INVENTOR(S): Llinas-Brunet, Montse; Gorys, Vida J.
PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003064455	A2	20030807	WO 2003-CA89	20030124
WO 2003064455	A3	20040205		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2369711	AA	20030730	CA 2002-2369711	20020130
EP 1472278	A2	20041103	EP 2003-700743	20030124
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003007297	A	20041221	BR 2003-7297	20030124
PRIORITY APPLN. INFO.:			CA 2002-2369711	A 20020130
			WO 2003-CA89	W 20030124

OTHER SOURCE(S): MARPAT 139:164979
GI

L47 ANSWER 24 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I

AB **Macrocyclic** peptides I [R1 is OH or NHSO2R1A, where R1A is (cyclo)alkyl, alkylcycloalkyl, or aryl which are optionally substituted from 1 to 3 times with halo, cyano, nitro, alkoxy, etc.; R2 is cycloalkyl] or their pharmaceutically-acceptable salt were prepared as inhibitors of the HCV NS3 protease. Thus, I (R1 = OH, R2 = cyclopentyl) was prepared and shown to have IC50 < 0.01 μM in the NS3-NS4A protease assay and EC50 < 0.01 μM in the cell-based HCV RNA replication assay.

L47 ANSWER 25 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

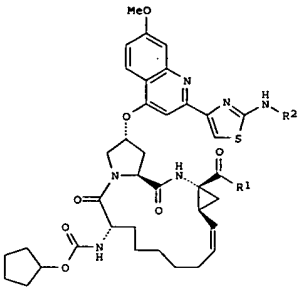
from 1 to 3 times with halo, cyano, nitro, alkoxy, etc.; R2 is cycloalkyl] or their pharmaceutically-acceptable salt were prepd. as inhibitors of the HCV NS3 protease. Thus, I (R1 = OH, R2 = cyclopentyl) was prepd. and shown to have IC50 < 0.01 μM in the NS3-NS4A protease assay and EC50 < 0.01 μM in the cell-based HCV RNA replication assay.

L47 ANSWER 25 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:950022 HCAPLUS
DOCUMENT NUMBER: 140:16973
TITLE: Preparation of **macrocyclic** peptides which are active against hepatitis C virus
INVENTOR(S): Llinas-Brunet, Montse; Gorys, Vida J.
PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 320,978.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003224977	A1	20031204	US 2003-353894	20030129
CA 2369711	AA	20030730	CA 2002-2369711	20020130
US 2003181363	A1	20030925	US 2002-320978	20021217
PRIORITY APPLN. INFO.:			CA 2002-2369711	A 20020130
			US 2002-320978	A2 20021217

OTHER SOURCE(S): MARPAT 140:16973
GI



I

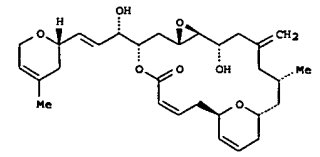
AB **Macrocyclic** peptides I [R1 is OH or NHSO2R1A, where R1A is (cyclo)alkyl, alkylcycloalkyl, or aryl which are optionally substituted

L47 ANSWER 26 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN

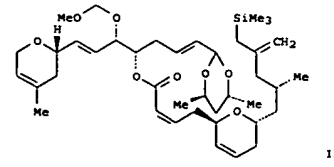
ACCESSION NUMBER: 2003:238326 HCAPLUS
DOCUMENT NUMBER: 138:271451
TITLE: Preparation of laulimalide and its derivatives for pharmaceutical uses
INVENTOR(S): Mulzer, Johann; Enev, Valentin S.
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: Eur. Pat. Appl., 58 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1295886	A1	20030326	EP 2001-250331	20010920
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
WO 2003024975	A1	20030327	WO 2002-EP10546	20020919
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			EP 2001-250331	A 20010920

OTHER SOURCE(S): MARPAT 138:271451
GI



I



II

L47 ANSWER 26 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

AB Laulimalide (I) and its deriva. were prepared for a variety of therapeutic uses, such as treatment of cancer, such as solid tumors and leukemia, autoimmune diseases, such as psoriasis, and multiple sclerosis, chemotherapeutically induced alopecia and mucositis, cardiovascular diseases, such as stenosis, arteriosclerosis and restenosis, infectious diseases caused by unicellular parasites, such as Trypanosoma, Toxoplasma or Plasmodium, or nephrol. diseases caused by fungi, such as glomerulonephritis, chronical neurodegenerative diseases, such as Huntington's disease, amyotropical lateral sclerosis, Parkinson disease, AIDS dementia and Alzheimer's diseases, acute neurodegenerative disease, such as ischemia of the brain and neurotrauma, viral infections, such as Cytomegalovirus infections, herpes, hepatitis B and C, and HIV diseases. Thus, laulimalide was prepared via a multistep synthetic sequence which included formation of the core **macrocyclic** ring by intramol. cyclization of protected aldehyde II using EtAlCl2 in CH2Cl2. Biol. testing data fop the prepared laulimalide deriva. were not presented.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L47 ANSWER 27 OF 39 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2003234331 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12671967
TITLE: **Macrocyclic** inhibitors of the NS3 protease as potential therapeutic agents of **hepatitis** C virus infection.
AUTHOR: Tsantrizos Youla S; Bolger Gordon; Bonneau Pierre; Cameron Dale R; Goudreau Nathalie; Kukolj George; LaPlante Steven R; Llinas-Brunet Montse; Nar Herbert; Lamarre Daniel
CORPORATE SOURCE: Department of Chemistry, Boehringer Ingelheim, Canada, Ltd., Research and Development, 2100 Cunard Street, Laval, PQ H7S 2G5, Canada.. ytsantrizos@lav.boehringer-ingelheim.com
SOURCE: Angewandte Chemie (International ed. in English), (2003 Mar 28) 42 (12) 1356-60.
Journal code: 0370543. ISSN: 0570-0833.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030522
Last Updated on STN: 20030813
Entered Medline: 20030812

L47 ANSWER 28 OF 39 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN

ACCESSION NUMBER: 2003512862 EMBASE
TITLE: **Macrocyclic** inhibitor for **hepatitis** C.
AUTHOR: Brazil M.
SOURCE: Nature Reviews Drug Discovery, (2003) Vol. 2, No. 12, pp. 945.
Refs: 1
ISSN: 1474-1776 CODEN: NRDDAG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
ENTRY DATE: Entered STN: 20040105
Last Updated on STN: 20040105
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L47 ANSWER 29 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:994331 HCAPLUS
TITLE: Antiviral drugs: **Macrocyclic** inhibitor for **hepatitis C**
AUTHOR(S): Brazil, Melanie
SOURCE: Nature Reviews Drug Discovery (2003), 2(12), 945
CODEN: NRDDAG; ISSN: 1474-1776
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; **News** Announcement
LANGUAGE: English
AB Unavailable
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L47 ANSWER 30 OF 39 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003401974 EMBASE
TITLE: Antiviral Research - 15th International Conference: HBV and HCV therapies: 17-21 March 2002, Prague, Czech Republic.
AUTHOR: Smee D.F.
CORPORATE SOURCE: D.F. Smee, Institute for Antiviral Research, ADVS Dept., Utah State University, UMC 5600, Logan, UT 84322-5600, United States. dsmee@cc.usu.edu
SOURCE: IDrugs, (2002) Vol. 5, No. 5, pp. 392-396.
ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
048 Gastroenterology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 20031023
Last Updated on STN: 20031023
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L47 ANSWER 31 OF 39 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2003401955 EMBASE
TITLE: Inhibitors of hepatitis C - A review of the recent patent literature.
AUTHOR: Zhang X.
CORPORATE SOURCE: X. Zhang, Experimental Station, Department of Chemistry, Bristol-Myers Squibb Pharmaceutical, Wilmington, DE 19880, United States. xiaojun.zhang@bms.com
SOURCE: IDrugs, (2002) Vol. 5, No. 2, pp. 154-158.
Refs: 34
ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
030 Pharmacology
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20031023
Last Updated on STN: 20031023
AB A review of the patent literature for inhibitors of hepatitis C virus (HCV) is presented for the period of January 2001 to December 2001. This review focuses on inhibitors of virally encoded enzymes/proteins, especially HCV NS3 serine protease and NS5B RNA-dependent RNA polymerase (RDRP), both of which have emerged as primary anti-HCV targets as a result of detailed understanding of their biological functions and the high quality structural information available. A number of potent small molecule inhibitors for these enzymes have been disclosed during this period of time. Inhibitors of other virally encoded enzymes have also been reported, but in lower numbers. With recent advances in obtaining a stable HCV cell-based assay to facilitate screening and selection of inhibitors, it is highly likely that effective small molecule antiviral therapies for HCV infection should soon emerge. .COPYRGT. PharmaPress Ltd.

L47 ANSWER 32 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:903883 HCAPLUS
DOCUMENT NUMBER: 136:31680
TITLE: Euphorbiaceae macrocyclic diterpenes for the treatment of inflammation
INVENTOR(S): Aylward, James Harrison; Parsons, Peter Gordon; Suhrbier, Andreas; Turner, Kathleen Anne
PATENT ASSIGNEE(S): Peplin Research Pty. Ltd., Australia
SOURCE: PCT Int. Appl., 172 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001093885	A1	20011213	WO 2001-AU680	20010607
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2411596	AA	20011213	CA 2001-2411596	20010607
AU 752435	B2	20020919	AU 2001-63662	20010607
EP 1296698	A1	20030402	EP 2001-937873	20010607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001011458	A	20030624	BR 2001-11458	20010607
JP 2003535138	T2	20031125	JP 2002-501456	20010607
NZ 522426	A	20040528	NZ 2001-522426	20010607
US 2003171337	A1	20030911	US 2002-315318	20021209
PRIORITY APPLN. INFO.:			AU 2000-8017 A	20000607
			WO 2001-AU680 W	20010607

OTHER SOURCE(S): MARPAT 136:31680
AB The invention relates generally to chemical agents useful in the treatment and prophylaxis of inflammatory conditions or in the amelioration of symptoms resulting from or facilitated by an inflammatory condition in a mammalian animal, including humans and primates, non-mammalian animal, and avian species. More particularly, the invention provides a chemical agent of the macrocyclic diterpene family obtaining from a member of the Euphorbiaceae family of plants or botanical or horticultural relatives thereof or derivs. or chemical analogs or chemical synthetic forms of the agents for use in the treatment or prophylaxis of an inflammatory condition or in the amelioration of symptoms resulting from or facilitated by an inflammatory condition in a mammal, animal or avian species. The invention further provides a method for the prophylaxis or treatment of mammalian, animal or avian subjects for inflammatory conditions including chronic or transitory inflammatory conditions or for ameliorating the

L47 ANSWER 32 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
symptoms of an inflammatory condition by the topical or systemic administration of a macrocyclic diterpene obtainable from a member of the Euphorbiaceae family or botanical or horticultural relatives thereof or a deriv., chem. analog or chem. synthetic form of the agent. The chem. agent of the invention may be in the form of a purified compd., mixt. of compds., a precursor form of one or more of the compds. capable of chem. transformation into a therapeutically active agent, or be in the form of a chem. fraction, sub-fraction, or prepn. or ext. of the plant.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 33 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:903881 HCAPLUS
DOCUMENT NUMBER: 136:42795
TITLE: **Macrocyclic** diterpenes for treatment and prophylaxis of PKC-related conditions
INVENTOR(S): Aylward, James Harrison; Parsons, Peter Gordon; Suhrbier, Andreas; Turner, Kathleen Anne
PATENT ASSIGNEE(S): Peplin Research Pty. Ltd., Australia
SOURCE: PCT Int. Appl., 215 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001093884	A1	20011213	WO 2001-AU679		20010607
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2411642	AA	20011213	CA 2001-2411642		20010607
AU 752462	B2	20020919	AU 2001-63661		20010607
EP 1296697	A1	20030402	EP 2001-937872		20010607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
BR 2001011423	A	20030429	BR 2001-11423		20010607
JP 2003535137	T2	20031125	JP 2002-501455		20010607
NZ 522425	A	20040528	NZ 2001-522425		20010607
US 2003166613	A1	20030904	US 2002-315288		20021209
PRIORITY APPLN. INFO.:			AU 2000-8017	A	20000607
			WO 2001-AU679	W	20010607

OTHER SOURCE(S): MARPAT 136:42795
AB The present invention relates generally to chemical agents useful in the treatment and prophylaxis of protein kinase C (PKC)-related conditions in mammals, including humans and primates, non-mammalian animals and avian species. More particularly, the present invention provides a chemical agent of the **macrocyclic** diterpene family obtainable from a member of the Euphorbiaceae family of plants or botanical or horticultural relatives thereof or derivs. or chemical analogs or chemical synthetic forms of the agents for use in the treatment or prophylaxis of PKC-related conditions in mammalian, animal and avian subjects. The subject chemical agents are also useful for modulating expression of genetic sequences including promotion and other regulatory sequences. The present invention further

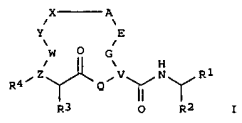
L47 ANSWER 33 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
contemplates a method for the prophylaxis and/or treatment in mammalian, animal or avian subjects with PKC-related conditions by the topical or systemic administration of a **macrocyclic** diterpene obtainable from a member of the Euphorbiaceae family of plants or their botanical or horticultural derivs. or a deriv., chem. analog or chem. synthetic form of the agent. The chem. agent of the present invention may be in the form of a purified compd., mixt. of compds., a precursor form of one or more of the compds. capable of chem. transformation into a therapeutically and/or genetically active agent or in the form of a chem. fraction, sub-fraction, prepn. or ext. of the plant. For example, an exts. of Euphorbia peplus sap (PEP003) reduced replication kinetics of HIV-1 virus in infected T-cells in a dose dependent manner. PEP003 at concns. of 500, 50, and 5 nM reduced the replication rate by approx. 99.9%, 95% and 47%, resp., relative to untreated, infected cells. Also, diterpene esters obtained from E. peplus activated human peripheral blood leukocytes to produce, in a PKC-dependent manner, phagocytosis and respiratory burst which are potentially lethal to microorganisms and other cells, e.g., tumor cells.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 34 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:798207 HCAPLUS
DOCUMENT NUMBER: 135:344735
TITLE: Preparation of **macrocyclic** NS3-serine protease inhibitors of **hepatitis C** virus comprising alkyl and aryl alanine p2 moieties
INVENTOR(S): Venkatraman, Srikanth; Chen, Kevin X.; Arasappan, Ashok; Njoroge, F. George; Girijavallabhan, Viyyoor M.; Chan, Tin-Yau; McKittrick, Brian A.; Prongay, Andrew J.; Madison, Vincent S.
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 218 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001081325	A2	20011101	WO 2001-US12530		20010417
WO 2001081325	A3	20020801			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
CA 2406532	AA	20011101	CA 2001-2406532		20010417
US 2002016294	A1	20020207	US 2001-836636		20010417
BR 2001010104	A	20030107	BR 2001-10104		20010417
EP 1274724	A2	20030115	EP 2001-927142		20010417
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2003531199	T2	20031021	JP 2001-578418		20010417
NZ 521456	A	20040730	NZ 2001-521456		20010417
ZA 2002008014	A	20040212	ZA 2002-8014		20021004
NO 2002005030	A	20021218	NO 2002-5030		20021018
PRIORITY APPLN. INFO.:			US 2000-198204P	P	20000419
			WO 2001-US12530	W	20010417

OTHER SOURCE(S): MARPAT 135:344735
GI

L47 ANSWER 34 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



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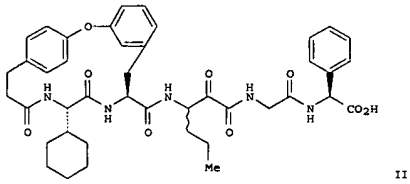


II

AB **Macrocyclic** compds. I [E, X, Y may be independently present or absent, and if present may be (un)substituted (cyclo)alkyl, aryl, heteroalkyl, heteroaryl, ether, amino, sulfide, sulfone, amide, sulfonamide, urea, carbamate, hydrazide, carbonyl, etc.; R1 = acyl or boryl groups; Z = O, N, or CH; W = null, CO, CS, SO2, C:NR (R = H, alkyl, cycloalkyl, aryl, etc.); Q = (NR)p (p = 0-6), O, S, CH2, CHR, CRR' (R' = any group given for R) or a double bond toward V; A = O, CH2, (CHR)p, (CHRCHR')p, (CRR')p, NR, S, SO2, CO or a bond; G = (CH2)p, (CHR)p, (CRR')p, NR, O, S, SO2, SO2NH, CO or a bond towards E or V; R2, R3, R4 = H, (un)substituted (hetero)alkyl, -aryl or -cycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, etc.], including enantiomers and pharmaceutically acceptable salts, were prepared as **hepatitis** C virus (HCV) protease inhibitors. Thus, peptide II was prepared by a multistep procedure involving cyclization of intermediate cyclopentadiene-η6-ruthenium-4-chlorophenylpropionic acid-cyclohexylglycine-m-tyrosine-OMe. II showed Ki = 0.001-1.0μM in the HCV protease assay. The invention also discloses pharmaceutical compns. comprising I as well as methods of using them to treat disorders associated with the HCV protease.

L47 ANSWER 35 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:763001 HCAPLUS
DOCUMENT NUMBER: 135:318715
TITLE: Preparation of macrocyclic NS3-serine protease inhibitors of hepatitis C virus comprising n-cyclic p2 moieties
INVENTOR(S): Chen, Kevin X.; Arasappan, Ashok; Venkatraman, Srikanth; Parekh, Tejal N.; Gu, Haining; Njoroge, F. George; Girijavallabhan, Viyyoor M.; Ganguly, Ashit; Saksena, Anil; Jao, Edwin; Yao, Nanhua H.; Prongay, Andrew J.; Madison, Vincent S.; Vibulbhan, Bancha
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 402 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077113	A2	20011018	WO 2001-US10869	20010403
WO 2001077113	A3	20020620		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2405521	AA	20011018	CA 2001-2405521	20010403
US 2002107181	A1	20020808	US 2001-825399	20010403
US 6846802	B2	20050125		
EP 1268525	A2	20030102	EP 2001-926601	20010403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001009861	A	20030610	BR 2001-9861	20010403
JP 2003530401	T2	20031014	JP 2001-575586	20010403
NZ 521455	A	20040625	NZ 2001-521455	20010403
ZA 2002007845	A	20040211	ZA 2002-7845	20020930
NO 2002004797	A	20021204	NO 2002-4797	20021004
PRIORITY APPLN. INFO.:			US 2000-194607P P	20000405
			WO 2001-US10869 W	20010403

OTHER SOURCE(S): MARPAT 135:318715
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [wherein X and Y = independently (cyclo)alkyl, heterocalkyl, (aryl)heteroaryl, alkyl(hetero)aryl, substituted ether, sulfide, sulfone, amide, sulfonamide, urea, carbamate, hydrazide, carbonyl, etc.; R1 = CHO, acyl, or (un)substituted carboxy, carbamoyl, boryl, etc.; Z = O, N, or CH, W = null or CO, CS, or SO2; Q = null or CH, N, P, (CH2)p, (CHR)p, (CRR')p, O, NR, S, or SO2; A = O, CH2, (CHR)p, (CHRCHR')p, (CRR')p, NR, S, SO2, or a bond; E = CH, N, CR, or a double bond toward A, L, or G; G = null or (CH2)p, (CHR)p, or (CRR')p; J = null or CH, CR, O, S, or NR; M = null or O, NR, S, SO2, *(CH2)p, (CHR)p, (CHRCHR')p, or (CRR')p; p = 0-6; R, R', R2, R3, and R4 = independently H, (cyclo)alkyl, alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, CHO, CN, NO2, O, N, S, P, etc.] were prepd. as hepatitis C virus (HCV) protease inhibitors. For example, II (multi-step prepn. given) was cyclized, deesterified, and coupled with III•HCl (prepn. given) to give the macrocyclic hydroxyamide intermediate. Oxidn. using Des-Martin reagent followed by flash chromatog. afforded two diastereomers IV in 82% combined yield. The (S)-isomer inhibited NS3-serine protease HeLa/Huh7 co-transfected cells with a Ki of 2 μM. The invention also discloses pharmaceutical compns. comprising I as well as methods of using them to treat disorders assocd. with the HCV protease.

L47 ANSWER 36 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:129915 HCAPLUS
DOCUMENT NUMBER: 134:174845
TITLE: Method for detecting enzyme-catalyzed cyclization and identifying peptidase inhibitors
INVENTOR(S): Bartlett, Paul A.; Burger, Matthew T.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: U.S., 14 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6190920	B1	20010220	US 1997-967910	19971112
PRIORITY APPLN. INFO.:			US 1997-967910	19971112

OTHER SOURCE(S): MARPAT 134:174845
AB A method for detecting cyclization of acyclic compds. is disclosed. The method comprises (a) contacting a peptidase-containing sample with NH2-R1-X-R2-CO-Y (CO-Y = carboxylic acid, ester, or amide which can be acylated or hydrolyzed by the peptidase; R1,R2 = ≥1 amino acid residues; one of R1 amino acids is linked to a dye or a resin and one of R2 amino acids is linked to a resin or dye such that a dye is attached at one side of X and a resin in attached to the other side of X; X = a group cleavable under conditions which do no cleave peptide bonds, e.g., ester, disulfide bond, cis diol, carbonate); (b) contacting the product of step (a) with an X-cleaving agent; (c) isolating the resin; and (d) determining the presence or absence of the dye mol. on the isolated resin. Thus, cyclization of the acyclic compound and presence of the peptidase is indicated by retention of the dye mol. on the resin. The invention also relates to using the above assay in screening for macrocyclic peptidase inhibitors. This method is useful for screening a combinatorial library of compds.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 37 OF 39 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2001244864 EMBASE
TITLE: Preface.
AUTHOR: Fairlie D.P.
CORPORATE SOURCE: D.P. Fairlie, Centre for Drug Design/Development, University of Queensland, Brisbane, QLD 4072, Australia
SOURCE: Current Medicinal Chemistry, (2001) Vol. 8, No. 8, pp. xxx.
ISSN: 0929-8673 CODEN: CMCHE7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 20010726
Last Updated on STN: 20010726
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

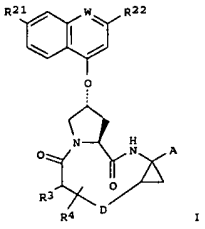
L47 ANSWER 38 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:725652 HCAPLUS
DOCUMENT NUMBER: 133:296659
TITLE: Preparation of **macrocyclic** peptides active against the **hepatitis** C virus
INVENTOR(S): Tsantrizos, Youla S.; Cameron, Dale R.; Faucher, Anne-marie; Ghiro, Elise; Goudreau, Nathalie; Halmos, Teddy; Llinas-brunet, Montse
PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
SOURCE: PCT Int. Appl., 154 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059929	A1	20001012	WO 2000-CA353	20000403
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2367127	AA	20001012	CA 2000-2367127	20000403
CA 2367127	C	20050118		
EP 1169339	A1	20020109	EP 2000-913999	20000403
EP 1169339	B1	20040929		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000009599	A	20020115	BR 2000-9599	20000403
TR 200102878	T2	20020121	TR 2001-200102878	20000403
EE 200100516	A	20021216	EE 2001-516	20000403
NZ 515286	A	20040227	NZ 2000-515286	20000403
EP 1437362	A1	20040714	EP 2004-9264	20000403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
AT 277945	E	20041015	AT 2000-913999	20000403
AU 778390	B2	20041202	AU 2000-35480	20000403
RU 2247126	C2	20050227	RU 2001-129709	20000403
ZA 2001007862	A	20040401	ZA 2001-7862	20010925
BG 105970	A	20020531	BG 2001-105970	20011002
HR 2001000720	A1	20021231	HR 2001-720	20011004
NO 2001004857	A	20011031	NO 2001-4857	20011005

PRIORITY APPLN. INFO.: US 1999-128011P P 19990406
EP 2000-913999 A3 20000403
WO 2000-CA353 W 20000403

OTHER SOURCE(S): MARPAT 133:296659
GI

L47 ANSWER 38 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I

AB **Macrocyclic** peptides I [W = CH or N; R21 = H, halo, alkyl, cycloalkyl, haloalkyl, alkoxy, cycloalkoxy, hydroxy, or an amino group; R22 = H, halo, alkyl, cycloalkyl, haloalkyl, thioalkyl, alkoxy, cycloalkoxy, alkoxyalkyl, cycloalkyl, aryl or heteroaryl; R3 = hydroxy, NH2, aryl- or heteroarylamino, NHCOR32, CONHR32, CO2R32, where R32 is alkyl or cycloalkyl; D is a 5 to 10 atom saturated or unsatd. alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or NH or substituted imino; R4 = H or from one to three substituents at any carbon atom of chain D; A is an amide or carboxylic acid group or a pharmaceutically acceptable salt or ester; two diastereomers may exist at the cyclopropane moiety] were prepared which are active in-vitro and in cellular assays against the NS3 protease of the **hepatitis** C virus . Thus, **macrocyclic** peptide I [W = N; R21, R22, R4 = H; A = CO2H; R3CH-D = (S)-(Me3CO2CNH)CH(CH2)3CH:CH(CH2)2-E (syn to acid)] was prepared and showed IC50 > 0.1 μM in the full-length NS3-NS4A heterodimer protein fluorogenic assay.

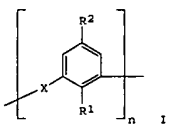
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 39 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:400876 HCAPLUS
DOCUMENT NUMBER: 121:876
TITLE: Inhibition and treatment of infection by enveloped virus with calix(n)arene compounds
INVENTOR(S): Hwang, Kou M.; Qi, You Mao; Liu, Su Ying; Choy, William; Chen, Jen
PATENT ASSIGNEE(S): Genelabs Technologies, Inc., USA
SOURCE: PCT Int. Appl., 162 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9403164	A1	19940217	WO 1993-US7366	19930805
W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5441983	A	19950815	US 1992-928108	19920806
AU 9348033	A1	19940303	AU 1993-48033	19930805
CN 1100302	A	19950322	CN 1994-101193	19940203

PRIORITY APPLN. INFO.: US 1992-928108 A2 19920806
US 1993-72566 A2 19930604
US 1991-647469 A2 19910129
US 1991-647720 A2 19910129
US 1991-791920 A2 19911113
WO 1993-US7366 W 19930805

OTHER SOURCE(S): MARPAT 121:876
GI



I

AB Cell infection by an enveloped virus is inhibited by administering to an infection site a therapeutically effective amount of a calix(n)arene compound derivatized, at its ring positions meta to the bridge attachments to the ring, with a polar substituent having a terminal carboxylate, phosphate,

L47 ANSWER 39 OF 39 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
or sulfonate group, including esters and amides which are cleavable in vivo. The compd. may be administered orally or topically, e.g., for treatment of herpes virus. The invention also includes a method of inhibiting infection by sexually transmitted enveloped viruses, by topically administering to an area of likely sexual contact a compn. contg. a prophylactically effective amt. of a **macrocyclic** compd. such as described above. A phys. barrier type device (e.g., condom, diaphragm, or cervical sponge) in combination with the above type compds. dissolved in a pharmaceutical vehicle for use in inhibiting infection by a sexually transmitted enveloped virus is also disclosed. Y-1 (I, R1 = OH; R2 = SO3; X = CH2; n = 8), applied topically as part of a lubricating jelly formulation, inhibited infection of cells with herpes simplex virus types 1 and 2 and HIV-1 strains.

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=> fil marpat
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    82.57     263.68

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -13.87     -16.06

FILE 'MARPAT' ENTERED AT 15:19:21 ON 04 APR 2005
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FILE CONTENT: 1988-PRESENT (VOL 142 ISS 14)(20050401/ED)

MOST RECENT CITATIONS FOR PATENTS FROM FIVE MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US     6841675 11 JAN 2005
DE    10351736 13 JAN 2005
EP     1498449 19 JAN 2005
JP 2005019756 20 JAN 2005
WO 2005018569  3 MAR 2005

Structure search limits have been raised.  See HELP SLIMIT for the new,
higher limits.

=> => d l49 que stat;d 1-4
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.
L49           4 SEA FILE=MARPAT SSS FUL L1

100.0% PROCESSED     37 ITERATIONS                          4 ANSWERS
SEARCH TIME: 00.00.01
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L49 ANSWER 1 OF 4 MARPAT COPYRIGHT 2005 ACS on STN
AN 141:380136 MARPAT
TI Process for preparing macrocyclic compounds
IN Donsbach, Kai; Ecker, Dieter; Frutos, Rogelio Perez; Gallou, Fabrice; Gutheil, Dieter; Haddad, Nizar; Hagenkoetter, Robert; Kemmer, Dirk; Kroeber, Jutta; Nicola, Thomas; Schnaubelt, Juergen; Schul, Michael; Simpson, Robert Donald; Wei, Xudong; Winter, Eric; Xu, Yibo; Yee, Nathan K.; Brandenburg, Joerg
PA Boehringer Ingelheim International, G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004092203	A2	20041028	WO 2004 US10476	20040406
	WO 2004092203	A3	20041209		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2005049187	A1	20050303	US 2004-818657	20040406
PRAI	US 2003-461662P		20030410		

L49 ANSWER 2 OF 4 MARPAT COPYRIGHT 2005 ACS on STN
AN 140:400031 MARPAT
TI Macrocyclic compound-containing compositions for the treatment of infection by Flaviviridae viruses
IN Lamarre, Daniel; Lagace, Lisette
PA Boehringer Ingelheim International GmbH, Germany
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004039833	A1	20040513	WO 2003-CA1634	20031024
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI	US 2002-421900P		20021029		
	US 2003-442769P		20030127		
RE.CNT	8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT				

L49 ANSWER 3 OF 4 MARPAT COPYRIGHT 2005 ACS on STN
AN 140:357673 MARPAT
TI Preparation of macrocyclic peptides active against the hepatitis C virus
IN Llinas-Brunet, Montse; Bailey, Murray D.
PA Boehringer Ingelheim International G.m.b.h., Germany
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004037855	A1	20040506	WO 2003-CA1604	20031020
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI	US 2002-421414P		20021025		
	US 2002-433820P		20021216		
	US 2003-442768P		20030127		

L49 ANSWER 4 OF 4 MARPAT COPYRIGHT 2005 ACS on STN
AN 139:69527 MARPAT
TI Preparation of macrocyclic compounds as inhibitors of hepatitis C virus
IN Campbell, Jeffrey Allen; Good, Andrew Charles
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 225 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003053349	A2	20030703	WO 2002-US39926	20021213
	WO 2003053349	A3	20040115		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004038872	A1	20040226	US 2002-317451	20021212
	US 6867185	B2	20050315		
	EP 1455809	A2	20040915	EP 2002-795860	20021213
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
PRAI	US 2001-344080P		20011220		
	US 2002-382103P		20020520		
	WO 2002-US39926		20021213		

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	63.51	327.19

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-16.06

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